ABBOTT

Corporate Regulatory Affairs

Abbott Laboratories
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100 Abbott Park Road
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April 29, 1998

The Food and Drug Administration
Dockets Management Branch (HFA-305)
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

RE: Bulk Drug Substances to be Used in Pharmacy Compounding; Request for Nominations [Docket No. 98N-0182]

Dear Sirs or Madams:

Per the enclosed Federal Register announcement, Abbott Laboratories submits for nomination two bulk drug substances - Taurine and Glutamine. Detailed packages on each drug are also enclosed.

We appreciate the opportunity to contribute to this process. If there are any questions on this package please feel free to contact me as shown below.

Yours truly,

Frank Pokrop,
Dir. Corp. Regulatory Affairs
(847) 937-8473
Fax: 847-938-3106

Enclosures:

1. Federal Register Announcement, April 7, 1998
2. Bulk Drug Information - Taurine
3. Bulk Drug Information - Glutamine

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98N-0182

NOM1

Federal Register

Tuesday, April 7, 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Bulk Drug Substances To Be Used in Pharmacy Compounding; Request for Nominations

AGENCY: Food and Drug Administration; Public Health Service
ACTION: Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
[Docket No. 98N-0182]

Bulk Drug Substances To Be Used in Pharmacy Compounding; Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for nominations.

SUMMARY: The Food and Drug Administration (FDA) is preparing to develop a list of bulk drug substances (bulk drugs) that may be used in pharmacy compounding that do not have a United States Pharmacopeia (USP) or National Formulary (NF) monograph and are not components of approved drugs. FDA is taking this action in accordance with provisions in the Food and Drug Administration Modernization Act of 1997 (FDAMA). To identify candidates for this bulk drugs list, FDA is encouraging interested groups and individuals to nominate specific bulk drug substances and is describing the information that should be provided to the agency in support of each nomination.

DATES: Nominations must be received by June 8, 1998, to receive consideration for inclusion on the bulk drugs list. Nominations received after this date will receive consideration for subsequent amendments to the list.

ADDRESSES: Send nominations to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Robert J. Tonelli, Center for Drug Evaluation and Research (HFD-332), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-0101.

SUPPLEMENTARY INFORMATION: President Clinton signed FDAMA (Pub. L. 105- 115) into law on November 21, 1997. One of the issues addressed in this new legislation is the applicability of the Federal Food, Drug, and Cosmetic Act (the act) to the practice of pharmacy compounding. Compounding involves a process whereby a pharmacist or physician combines, mixes, or alters ingredients to create a customized medication for an individual patient. Section 127 of FDAMA, which adds section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug

provisions of the act. Section 127 becomes effective 1 year from the date of the FDAMA's enactment (section 503A(b) of the act).

Section 127 contains several restrictions regarding the bulk drug substances{1} that may be used as ingredients in compounding and still qualify for the applicable exemptions. It provides, among other things, that such substances must comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapter on pharmacy compounding; if a monograph does not exist, they must be components of drugs approved by FDA; and if neither of those criteria are satisfied, they must appear on a list that FDA develops and issues through regulations (section 503A(b)(1)(A)(i)(I) through (b)(1)(A)(i)(III) of the act).

{1} The term ``bulk drug substance'' is defined in FDA's regulations at 21 CFR 207.3(a)(4) and incorporated in section 127 of FDAMA to mean ``any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.'' ----------

In accordance with the bulk drug provisions in section 127, FDA is preparing to develop a list of bulk drug substances that may be used in compounding that do not have a USP or NF monograph and are not components of approved drugs. To identify candidates for this list, FDA is seeking public input in the form of specific bulk drug nominations. All interested groups and individuals are encouraged to nominate specific bulk drug substances for inclusion on the list. FDA intends for this nomination process to serve as its principal means of identifying list candidates. After evaluating the nominations and, as required by Congress, consulting with the United States Pharmacopeial Convention, Inc., and an advisory committee on compounding (section 503A(d) of the act), FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following information about the bulk drug substance being nominated and the product(s) that will be compounded using such substance. If the information requested is unknown or unavailable, that fact should be noted accordingly.

Bulk Drug Substance

» Ingredient name;
» Chemical name;
» Common name(s);

» Chemical grade or description of the strength, quality, and purity of the ingredient;

» Information about how the ingredient is supplied (e.g., powder, liquid);

» Information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development; and

» A bibliography of available safety and efficacy data {2}, including any

relevant peer reviewed medical literature. ----------

{2} FDA recognizes that the available safety and efficacy data is unlikely to be of the same type, amount, or quality as would be required to support a new drug application, but this fact will not preclude a bulk drug substance from consideration for inclusion on the list.

Compounded Product

» Information about the dosage form(s) into which the drug substance will be compounded (including formulations);

» Information about the strength(s) of the compounded product(s);

» Information about the anticipated route(s) of administration of the compounded product(s);

» Information about the past and proposed use(s) of the compounded product(s), including the rationale for its use or why the compounded product(s), as opposed to a commercially available product, is necessary;

» Available stability data for the compounded product(s); and

» Additional relevant information.

FDA cannot guarantee that all drugs nominated during the comment period will be considered for inclusion on the first published bulk drugs list. Nominations received during the comment period that are supported by the most complete and relevant information, as set forth previously, will likely be evaluated first. Nominations that are not evaluated during this first phase will receive consideration for list amendments, as the development and issuance of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested groups and individuals should submit their bulk drug substance nominations to the Dockets Management Branch (address above). Two copies of the nominations are to be submitted, except that individuals may submit one copy. However, individuals are encouraged to consolidate their submissions through professional organizations. Nominations are to be identified with the docket number found in brackets in the heading of this document. Received nominations and supporting information will be treated as public information and will be available for inspection at the above address between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 1, 1998.

William B. Schultz,

Deputy Commissioner for Policy. [FR Doc. 98-9037 Filed 4-6-98; 8:45 am] BILLING CODE 4160-01-F

The Contents entry for this article reads as follows:

Human drugs:

*** END OF DOCUMENT ***

Candidates for Bulk Drug List - FDA Modernization Act Pharmacy Compounding

Bulk Drug Information

Ingredient Name: **Taurine**

Chemical Name: 2-aminoethanesulfonic acid

Common Name: Taurine

Chemical Grade: Per specifications attached

How Supplied: Powder

Foreign Pharmacopeia Status: Is not listed in EP nor JP

Submitted previously to USP: Unknown

Safety and Efficacy data bibliography: See reference list and abstracts attached

Compounded Product Information

Dosage Form: Sterile Injectable Solution

Strength: 2% to 5% solution of Taurine in Sterile Water for Injection to be further diluted with Total Parenteral Nutrition (TPN) Solution prior to administration for a total dose of 5 mg to 10 mg/ Kg body wt/ day

Route of Administration: Intravenous (IV)

Information on past and proposed uses; rationale for use: See attached articles

Why not use commercially available source?: Not available as a commercially available sterile solution supplement

Stability Data: Conservatively given 2 weeks expiration dating at refrigerated temperatures based on fact taurine is used in commericially available pediatric amino acid formulations and given 18 months expiration dating. Taurine is not currently available as a sterile solution supplement.

TITLE:

Taurine

SPECIFICATIONS:

Taurine	Not less than 98.5 percent and not more than 101.0 percent of C2 H7 N03 S, calculated on the dried basis.
Physical Examination (Containers) *	
Physical Examination (Contents) *	
Appearance	Powder.
Color	White.
State of Solution (Transmittance)	Not less than 95.0 percent transmittance.
Chloride	Not more than 0.01 percent.
Ammonium	Not more than 0.02 percent.
Sulfate	Not more than 0.01 percent.
Heavy Metals	Not more than 10 ppm.
Arsenic	Not more than 2 ppm.
Loss on Drying	Not more than 0.2 percent.
Residue on Ignition	Not more than 0.1 percent.
Pyrogen	Passes test.
Identification (Infrared)	Sample and standard spectra exhibit maxima only at the same wavelengths.

ADDITIONAL TESTING

Manufacturer's Name and Manufacturing Location	Must be documented and agree with Lot Uniformity sheet. Documentation must be maintained as a part of the record.
Certificate of Analysis	Must accompany each lot received and be maintained as a part of the record.

*Carried out by Abbott Incoming Drug Inspection Department according to departmental procedures.

NOTE: If desiccant bags are required in each container, the desiccant bags must not contact the raw drug material. They must be placed outside of the liner in the raw drug container. Desiccant bags may not be made of fiber generating materials. The number of desiccant bags must be identified on the outside of each container.

Packing and Marking: Pack, mark and label in accordance with all applicable regulations.

REFERENCES

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2. Wilmore DW, Dudrick SJ. Growth and Development of an Infant Receiving all Nutrients Exclusively by Vein. JAMA 1968; 203:860-4.

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8. Tulikoural I, HuiKuri K. Morphological Fatty Changes and Function of the Liver, Serum Free Fatty Acids and Triglycerides during Parenteral Nutrition. Scand J Gastroenterol 1982; 17:177-85.

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11. Brown MR, Putnam TC. Cholestasis Associated with Central Intravenous Nutrition in Infants. NY State J Med 1978; 78:27-30.

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17. Huxtable RJ. Physiological Actions of Taurine. Physiol Rev 1992; 72(1):101-63.

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22. Wang W-Y, Liaw K-Y. Effect of a Taurine-Supplemented Diet on Conjugated Bile Acids in Biliary Surgical Patients. JPEN 1991; 15:294-7.

23. Dorvil NP, Yousef IM, Tuchweber B. Taurine Prevents Cholestasis Induced by Lithocholic acid Sulfate in Guinea Pigs. Am J Clin Nutr 1983; 37:221-32.

24. Fouin-Fortunet H, LeQuernec L, Erlinger S et al. Hepatic Alterations During Total Parenteral Nutrition in Patients with Inflammatory Bowel Disease: A Possible Consequence of Lithocholate Toxicity. Gastroenterology 1982; 82:932-7.

25. Kopple JD, Vinton NE, Laidlaw SA et al. Effect of Intravenous Taurine Supplementation on Plasma, Blood Cells and Urine Taurine Concentrations in Adults Undergoing Long-Term Parenteral Nutrition. Am J Clin Nutr 1990; 52:846-53.

26. Roe DA, Weston MD. Potential Significance of Free Taurine in the Diet. Nature 1965; 205:287-8.

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DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1994 BIOSIS. All rts. reserv.
7730454 BIOSIS Number: 90098454
ANALYSIS AND HEAT STABILITY OF TAURINE IN MILK
SAIDI B; WARTHESEN J J
DEP. FOOD CHEM., IAV HASSAN II, RABAT, MOROCCO.
J DAIRY SCI 73 (7). 1990. 1700-1706. CODEN: JDSCA
Full Journal Title: Journal of Dairy Science
Language: ENGLISH
A method based on formation of the fluorescamine derivative of taurine and HPLC was developed for analysis of taurine in milk. Taurine in milk ranged from 2.4 to 12.0 mg/L. The degradation of taurine in taurine-fortified milk and in a buffered taurine and lactose solution (pH 6.7) was determined by heating at 80, 100, and 120.degree.. First-order reaction kinetics were observed for taurine losses in milk and buffered solution. Activation energies were 20.5 and 21.0 kcal/mol for milk and buffered solution, respectively. The taurine loss in milk seems to proceed through browning with the same degradation rate as lysine.

DIALOG(R)File 155:MEDLINE(R)
(c) format only 1994 Dialog Info.Svcs. All rts. reserv.
06413663 88058663
Liquid chromatographic determination of taurine in vitamin premix formulations.
Rao GN
Abbott Laboratories, Pharmaceutical Products Division, North Chicago, IL 60064.
J Assoc Off Anal Chem (UNITED STATES) Sep-Oct 1987, 70 (5) p799-801,
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A liquid chromatographic (LC) method is described for the determination of taurine in vitamin and vitamin-mineral premix formulations. The method involves extraction of taurine with 0.1 M bicarbonate buffer, followed by precolumn derivatization with dansyl chloride and LC using fluorescence detection. 6-Aminocaproic acid is used as an internal standard. A reverse phase analytical column and a mobile phase of 0.1 M acetate buffer solution (pH 7.2)-acetonitrile (75 + 25) are used. Vitamins, minerals, and other excipients in the premix formulations do not interfere in the determination. The method is simple, precise, and accurate.

DIALOG(R)File 74:Int.Pharm.Abs.
(c) 1994 Amer.Soc.of Hosp.Pharmacists Inc. All rts. reserv.
0084125 19-05124
Thermal decomposition of analytes, and conditions for transport of specific fragments in the TAS procedure
Grdinic, V.; Gross, S.; Grdinic, S.
Dept. of Chem., Faculty of Pharm. and Biochem., Univ. of Zagreb, Zagreb, Yugoslavia
Acta Pharm. Jugosl. 29:193-201 (4) 1979
Coden: APJUA8
Languages: English Summary Languages: Serbo-croatian
(13 References)
The thermal stability of taurine and buformin hydrochloride during thin layer chromatographic separation procedures based on thermal action and displacement (TAS procedure) was studied.
Factors such as the influence of the TAS oven, the duration of thermoextraction, the kinds and quantities of expellants and pyrolytic agents were investigated on the basis of identification of volatile substances with acidic, neutral and alkaline character.
Thompson (AA*)

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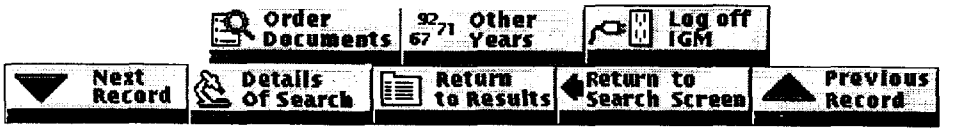
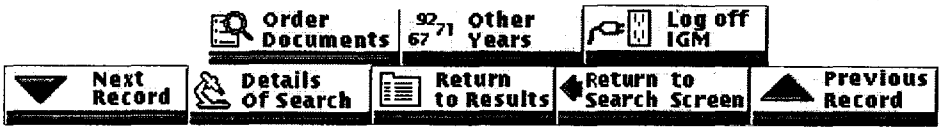


TITLE: Taurine in infant nutrition.
AUTHOR: Karan S
AUTHOR AFFILIATION: Department of Pediatrics, Niloufer Hospital for Women and Children, Red Hills, Hyderabad.
SOURCE: Indian J Pediatr 1991 May-Jun;58(3):311-6
NLM CIT. ID: 92039901
ABSTRACT: The importance of taurine in diet is poorly understood. The present evidence suggests that it is a conditionally essential aminoacid in man wherein deficiency states may result in adverse changes which will be improved with supplementation. It has a role in fat absorption in preterm infants and children with cystic fibrosis, retinal dysfunction in patients receiving TPN and those with blind loop gut syndromes. Taurine is also reported to improve maturation of ABER in pre-term infants and has a role in osmoregulation of CNS and may act as neuroinhibitor.
MAIN MESH SUBJECTS: *Diet
*Infant Nutrition
*Taurine/DEFICIENCY/METABOLISM/PHYSIOLOGY
ADDITIONAL MESH SUBJECTS: Human
Infant
PUBLICATION TYPES: JOURNAL ARTICLE
REVIEW
REVIEW, TUTORIAL
LANGUAGE: Eng
REGISTRY NUMBERS: 107-35-7 (Taurine)



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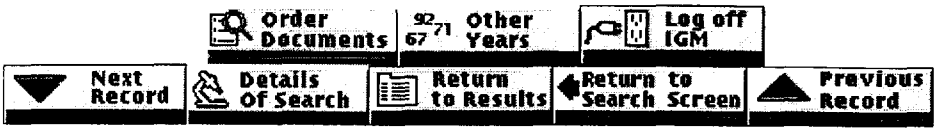

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TITLE: Effect of intravenous taurine supplementation on plasma, blood cell, and urine taurine concentrations in adults undergoing long-term parenteral nutrition.

AUTHOR: Kopple JD; Vinton NE; Laidlaw SA; Ament ME
AUTHOR AFFILIATION: Department of Medicine, School of Medicine, UCLA, Torrance 90509.

SOURCE: Am J Clin Nutr 1990 Nov;52(5):846-53
NLM CIT. ID: 91051308

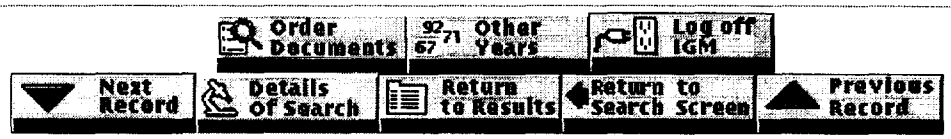
ABSTRACT: Thirty-four adults undergoing long-term parenteral nutrition (TPN) were treated either with or without intravenous taurine for less than or equal to 24 mo. Statistical comparisons were carried out in eight patients randomly assigned to receive intravenous taurine, usually 10 mg.kg-1.d-1, and 10 patients not receiving taurine. Compared with normal adults, baseline plasma taurine and urine taurine-creatinine ratios were decreased in both groups and platelet taurine was reduced in the taurine-treated group. During taurine treatment the mean of the mean values for taurine became normal in plasma and platelets and remained normal in erythrocytes, granulocytes, and lymphocytes; urine taurine-creatinine ratios rose to approximately five times normal. During follow-up, patients not given taurine had plasma, erythrocyte, and granulocyte taurine and urine taurine-creatinine ratios below normal values and the concentrations of taurine-treated patients. Their platelet taurine was also subnormal. Thus, 10 mg taurine.kg-1.d-1 intravenously normalizes plasma and blood cell taurine concentrations in long-term TPN patients.

MAIN MESH SUBJECTS: *Parenteral Nutrition, Total
Taurine/BLOOD/*PHARMACOLOGY/URINE
ADDITIONAL MESH SUBJECTS: Adult
Blood Platelets/CHEMISTRY
Comparative Study
Creatinine/URINE
Erythrocytes/CHEMISTRY
Female
Granulocytes/CHEMISTRY
Human
Infusions, Intravenous
Lymphocytes/CHEMISTRY
Male
Middle Age
Support, Non-U.S. Gov't
Support, U.S. Gov't, P.H.S.

PUBLICATION TYPES: CLINICAL TRIAL
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: Eng

REGISTRY NUMBERS: 107-35-7 (Taurine)
60-27-5 (Creatinine)



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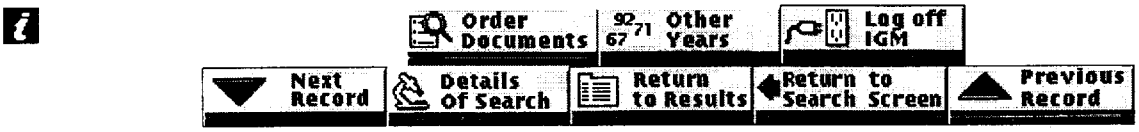

TITLE:	Taurine-supplemented total parenteral nutrition and taurine status of malnourished cancer patients.
AUTHOR:	Gray GE; Landel AM; Meguid MM
AUTHOR AFFILIATION:	Department of Surgery, University Hospital, SUNY Health Science Center, Syracuse 13210.
SOURCE:	Nutrition 1994 Jan-Feb;10(1):11-5
NLM CIT. ID:	94257924
ABSTRACT:	The status of plasma taurine and whether its concentration can be influenced by total parenteral nutrition (TPN) was determined in 51 malnourished fasting cancer patients after surgery and 7-14 days after starting TPN providing 41 +/- 2 kcal, 0.30 +/- 0.02 g N kg-1.day-1 and 40 mg pyridoxine. Plasma taurine was 50% lower in patients than in control subjects. Plasma taurine was significantly greater than baseline only after 14 days of TPN. We also studied the effects of surgery and taurine supplementation (8.6 mg.kg-1.day-1) on plasma and urine taurine concentrations in 12 malnourished patients. Preoperatively, all patients had normal plasma taurine concentrations; postoperatively, it was in the deficient range in 4 patients. Taurine-supplemented patients initially had higher than baseline concentrations; by day 10, none had subnormal levels. Subnormal taurine concentrations commonly occur in malnourished postoperative cancer patients; surgery further precipitates their fall. Plasma concentrations were maintained only with taurine-supplemented TPN.
MAIN MESH SUBJECTS:	Neoplasms/BLOOD/*COMPLICATIONS Nutrition Disorders/BLOOD/*COMPLICATIONS/*THERAPY *Parenteral Nutrition, Total/METHODS Taurine/*ADMINISTRATION & DOSAGE/*BLOOD/DEFICIENCY
ADDITIONAL MESH SUBJECTS:	Adult Aged Cysteine/BLOOD Female Human Male Methionine/BLOOD Middle Age Support, Non-U.S. Gov't
PUBLICATION TYPES:	CLINICAL TRIAL JOURNAL ARTICLE RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	Eng
REGISTRY	107-35-7 (Taurine)

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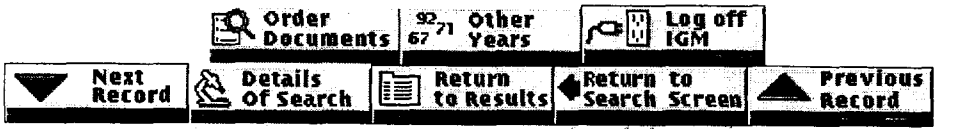
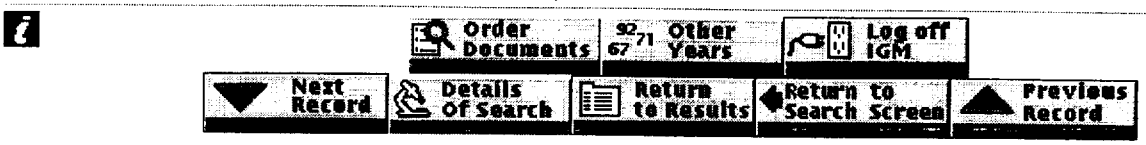


TITLE:	Effects of total parenteral nutrition using a solution enriched with branched-chain amino acids on experimental pancreatitis in rats.
AUTHOR:	Alhan E; Kucuktulu U; Ercin C; Calik A; Cinel A
AUTHOR AFFILIATION:	Department of Surgery, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey.
SOURCE:	Eur Surg Res 1997;29(5):382-9
NLM CIT. ID:	97464778
ABSTRACT:	The main purpose of this study was to investigate the influence of total parenteral nutrition enriched with branched-chain amino acids (BCAA) on acute pancreatitis (AP) induced by sodium taurocholate in rats. Total parenteral nutrition (TPN) increased the survival rate and serum calcium, and reduced serum urea, liver transaminase, acid phosphatase and lactate dehydrogenase levels, but it did not change the degree of pancreatic damage or serum amylase. Total plasma amino acid concentration and the concentrations of glutamate, glycine, alanine, taurine, valine, leucine, isoleucine, phenylalarine increased significantly after the induction of AP, but there was no difference between the control and therapy groups. Hyperglycemia occurred during the use of TPN. BCAA-enriched TPN can be used in the treatment of AP with few side effects.
MAIN MESH SUBJECTS:	Amino Acids, Branched-Chain/*ADMINISTRATION & DOSAGE Pancreatitis/BLOOD/PATHOLOGY/*THERAPY *Parenteral Nutrition, Total
ADDITIONAL MESH SUBJECTS:	Amino Acids/BLOOD Animal Male Osmolar Concentration Pancreas/PATHOLOGY Rats Rats, Sprague-Dawley Solutions
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Amino Acids) 0 (Amino Acids, Branched-Chain) 0 (Solutions)

NUMBERS: **4371-52-2 (Cysteine)**
7005-18-7 (Methionine)



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TITLE: Early metabolic treatment after liver transplant: amino acid tolerance.

AUTHOR: Iapichino G; Radrizzani D; Bonetti G; Codazzi D; Colombo A; Gridelli B; Langer M; Ronzoni G; Savioli M

AUTHOR AFFILIATION: Istituto Anestesiologia e Rianimazione dell'Universita, IRCCS Ospedale Maggiore, Milano, Italy.

SOURCE: Intensive Care Med 1995 Oct;21(10):802-7

NLM CIT. ID: 96128631

ABSTRACT: OBJECTIVE: We investigated the amino acid (AA) tolerance during Total Parenteral Nutrition (TPN) in adult patients undergone liver transplant (LTX). DESIGN: The treatment (Glucose and AA), induced on the 2nd postoperative day, was later maintained with 27 kcal/kg Ideal Body Weight (IBW) as glucose and 0.12 (12 patients: protocol #1), 0.18 (10 patients: protocol #2) and 0.25 g nitrogen (N)/kg IBW (13 patients: protocol #3) till end of the 6th postoperative day. The N intake was sequentially modified in protocol #2 and #3 to increase the supply of the amino acid (AA) that resulted in an infusion plasma level below the expected "normal" range (between 1 and 1.6 times the overnight fasting plasma level of volunteer). PATIENTS: 35 consecutive adult patients without diabetes and organ failures for the entire study period. MEASUREMENTS: Plasma AA profile was measured before LTX and at the last TPN day under continuous infusion. During #1 and #2 protocol, many AA resulted below or at the lower range of the norm while, during 0.25 gN/kg IBW infusion, the majority of the administered AA significantly increased with respect to reference values. Nevertheless, they remained in the "normal" plasma range indicating that they were supplied in an optimal amount (particularly the aromatic and sulphurated ones, potentially toxic if liver function is impaired, and the branched chain AA (BCAA) given at consistent dosage: 0.5 g/kg). Arginine resulted significantly increased (Arg: 1.9 times the reference) and cystine (Cys: 0.45), serine (Ser: 0.8) and taurine (Tau: 0.85) remained significantly lower than "normal" as well as the not administered citrulline (Cit: 0.58) and alfa amino butyric acid (Aba: 0.41). The AA (and calorie) load almost balanced the N losses during the 5th (0.411 +/- 0.038) and 6th study day (0.305 +/- 0.019 gN/kg). CONCLUSIONS: 0.25 gN/kg could be considered the minimum N load in the uncomplicated adult LTX recipients, for reassuring a balanced plasma AA pattern and body N turnover in the early postoperative phase.

MAIN MESH SUBJECTS: Amino Acids/ANALYSIS/*BLOOD/*THERAPEUTIC USE
*Energy Intake
Liver Transplantation/*ADVERSE EFFECTS/*PHYSIOLOGY
Parenteral Nutrition, Total/*METHODS

ADDITIONAL Adolescence

MESH SUBJECTS:	**Adult** **Comparative Study** **Drug Monitoring** **Female** **Human** **Male** **Middle Age** **Nutrition Assessment** **Reference Values** **Support, Non-U.S. Gov't**
PUBLICATION TYPES:	**CLINICAL TRIAL** **JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Amino Acids)**

National Library of Medicine: IGM Full Record Screen

TITLE: Taurine induces a long-lasting increase of synaptic efficacy and axon excitability in the hippocampus.

AUTHOR: Galarreta M; Bustamante J; Martin del Rio R; Solis JM
AUTHOR AFFILIATION: Departamento de Investigacion, Hospital Ramon y Cajal, Madrid, Spain.

SOURCE: J Neurosci 1996 Jan;16(1):92-102
NLM CIT. ID: 96110785

ABSTRACT: The physiological role of taurine, one of the most abundant free amino acids in the mammalian brain, is still poorly understood. We have found that bath application of the amino acid taurine induces two opposite actions on field excitatory synaptic potentials (fEPSP) recorded in the CA1 area of hippocampal slices: a decrease in fEPSP slope prevented by GABAA antagonists, and a long-lasting potentiation of fEPSP independent of GABAA or NMDA receptor activation. Two long-lasting processes account for this taurine-induced potentiation: (1) an increase in synaptic efficacy that is accompanied neither by modifications in the basic postsynaptic membrane electrical properties nor by those presynaptic changes involved in fEPSP paired-pulse facilitation; and (2) an increase in the axon excitability revealed by a reduction on the threshold for antidromic action potential activation. In addition, taurine perfusion also induces a long-lasting increase in intracellularly recorded EPSPs and monosynaptically activated IPSPs. A number of experimental observations such as temperature dependence, extracellular Na+ concentration dependence, and saturation studies, although they are not unequivocally conclusive, suggest that the taurine uptake system is required for the taurine-induced fEPSP potentiation. Our data describe a new taurine action defined as a potentiation of synaptic transmission due in part to an increment in presynaptic axon excitability and in synaptic efficacy.

MAIN MESH SUBJECTS:
Axons/*PHYSIOLOGY/ULTRASTRUCTURE
Hippocampus/CYTOLOGY/*PHYSIOLOGY
Synaptic Transmission/*PHYSIOLOGY
Taurine/PHARMACOLOGY/*PHYSIOLOGY

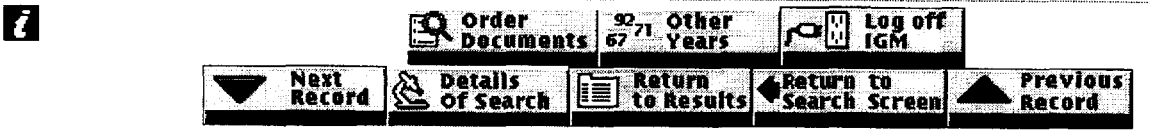
ADDITIONAL MESH SUBJECTS:
Animal
Drug Synergism
Electrophysiology
Evoked Potentials/PHYSIOLOGY
Female
Membrane Potentials/PHYSIOLOGY
Potassium Channels/ANTAGONISTS & INHIB
Rats
Rats, Sprague-Dawley

Receptors, GABA-A/ANTAGONISTS & INHIB/PHYSIOLOGY
Receptors, N-Methyl-D-Aspartate/PHYSIOLOGY
Support, Non-U.S. Gov't
Time Factors

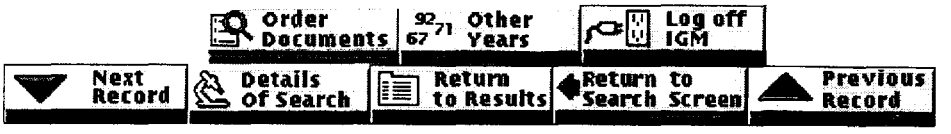
PUBLICATION TYPES: **JOURNAL ARTICLE**

LANGUAGE: **Eng**

REGISTRY NUMBERS: **0 (Potassium Channels)**
0 (Receptors, GABA-A)
0 (Receptors, N-Methyl-D-Aspartate)
107-35-7 (Taurine)

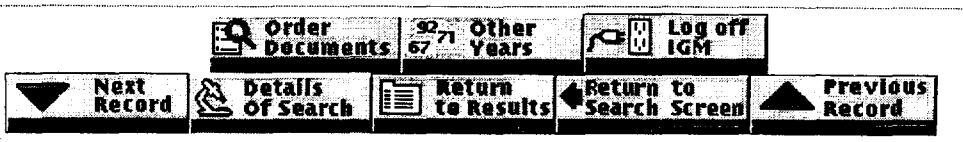


National Library of Medicine: IGM Full Record Screen

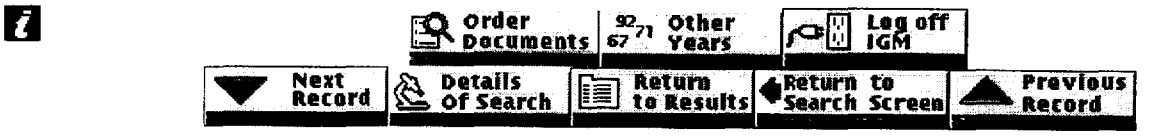


TITLE: [Role of taurine in neutrophil function]
AUTHOR: Masuda M; Horisaka K; Koeda T
SOURCE: Nippon Yakurigaku Zasshi 1984 Sep;84(3):283-92
NLM CIT. ID: 85052750
ABSTRACT: The influence of taurine on neutrophil phagocytic and bactericidal capacities and lysosomal enzyme-releasing ability was evaluated in the present study using neutrophils obtained from casein-elicited rat peritoneal exudates. Taurine was dissolved in drinking water at a concentration of 0.3%, and the solution was given to rats for 1-21 days (460 mg/kg/day). Taurine concentration in the serum increased with the term of its administration, while in the neutrophils, it increased significantly after administration for 1 or 3 days. When administered for 7 or 10 days, however, no difference was noted from the control group, but then the concentration remarkably increased after 21 days of administration. The bactericidal capacity of the neutrophils against Escherichia coli was strengthened as their concentration of taurine increased; phagocytic capacity was also strengthened. The release of myeloperoxidase following phagocytosis of yeasts increased with administration, while the release of beta-glucuronidase, lysozyme and lactate dehydrogenase, which are induced by N-formylmethionyl-leucyl-phenylalanine, were inhibited. The hypotonic hemolysis of erythrocytes was also inhibited. Taurine decreased the fluorescence depolarization of diphenylhexatriene, indicating an increase in membrane fluidity. These results suggested that taurine strengthens both phagocytic and bactericidal capacities of neutrophils by increasing the fluidity of neutrophil membrane and membrane stability and thus plays an important role in the mechanism of host defense.
MAIN MESH SUBJECTS: *Blood Bactericidal Activity/DRUG EFFECTS
Neutrophils/ENZYMOLOGY/*PHYSIOLOGY
Taurine/BLOOD/PHARMACOLOGY/*PHYSIOLOGY
ADDITIONAL MESH SUBJECTS: Animal
Cell Membrane/DRUG EFFECTS/PHYSIOLOGY
English Abstract
Lysosomes/ENZYMOLOGY
Male
Membrane Fluidity/DRUG EFFECTS
Phagocytosis/DRUG EFFECTS
Rats
Rats, Inbred Strains
PUBLICATION TYPES: JOURNAL ARTICLE
LANGUAGE: Jpn

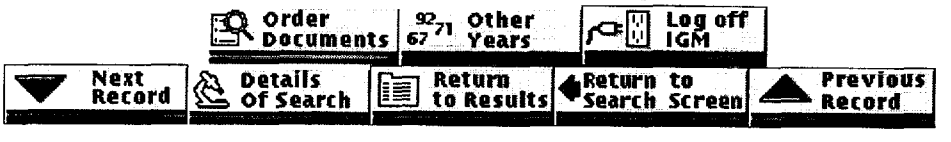
REGISTRY NUMBERS: **107-35-7 (Taurine)**



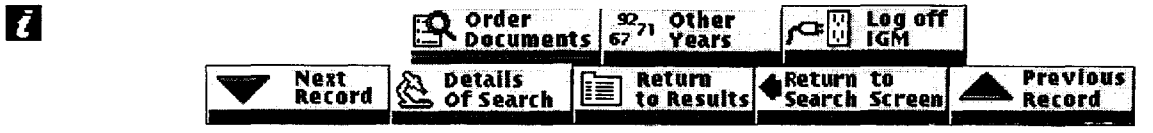
National Library of Medicine: IGM Full Record Screen



TITLE:	Taurine in the nutrition of the human infant.
AUTHOR:	Gaull GE
SOURCE:	Acta Paediatr Scand Suppl 1982;296:38-40
NLM CIT. ID:	83123119
ABSTRACT:	The precise biological role of taurine is unknown apart from its conjugation with bile acids and xenobiotics. Evidence is accumulating, however, that taurine may have a more general biological role in development and membrane stability. Furthermore, there is a dietary requirement for taurine in the human infant. Whether or not it is "essential" in man, awaits further study.
MAIN MESH SUBJECTS:	Infant Food/*ANALYSIS *Infant, Premature Milk, Human/*ANALYSIS Taurine/*ADMINISTRATION & DOSAGE/METABOLISM
ADDITIONAL MESH SUBJECTS:	Animal Cats Human Infant, Newborn Nutritional Requirements
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	107-35-7 (Taurine)



National Library of Medicine: IGM Full Record Screen



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TITLE: [Determination of taurine, L-glutamine, vitamin U and L-aspartic acid in pharmaceuticals by high-performance liquid chromatography with pre-column derivatization]

AUTHOR: Uehara S; Nojiri S; Takahashi M; Watanabe Y

AUTHOR AFFILIATION: Tokyo Metropolitan Research Laboratory of Public Health, Japan.

SOURCE: Yakugaku Zasshi 1994 Sep;114(9):697-703

NLM CIT. ID: 95055012

ABSTRACT: A pre-column derivatization method for the high-performance liquid chromatographic determination of taurine (1), L-glutamine (2), vitamin U (3) and L-aspartic acid (4) in pharmaceuticals has been developed. The optimum requirements for the derivatization conditions and the stability of resulting derivatives were discussed. The compounds were converted into DNT derivatives through the amino group by reaction with sodium 2,6-dinitro-4-trifluoromethylbenzenesulfonate (DNTS) in 50% sodium borate at 60 degrees C for 30 min (1), at 60 degrees C for 90 min (2), at 60 degrees C for 80 min (3) and at 80 degrees C for 90 min (4). After the reaction mixtures were acidified with dil. HCl, the derivatives were separated on a Cosmosil 3C18 (4.6 mm i.d. x 50 mm) column using 1% acetic acid-methanol (13:7) containing 2 mM sodium 1-heptanesulfonate as mobile phase with a ultra violet detector at 280 nm. The precisions of the analytical values expressed as the coefficient of variation were below 2.0%. The recoveries of 1-4 added to various commercial samples were in the range of 97.8-100.6%.

MAIN MESH SUBJECTS: Aspartic Acid/*ANALYSIS
Glutamine/*ANALYSIS
Taurine/*ANALYSIS
Vitamin U/*ANALYSIS

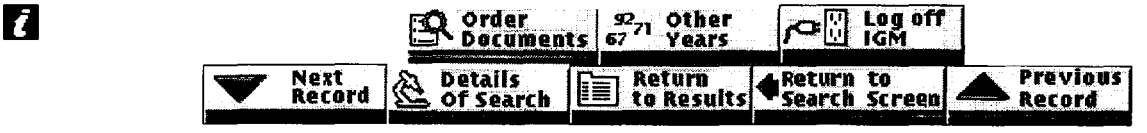
ADDITIONAL MESH SUBJECTS: Chemistry, Pharmaceutical/METHODS
Chromatography, High Pressure Liquid/METHODS
English Abstract
Support, Non-U.S. Gov't

PUBLICATION TYPES: JOURNAL ARTICLE

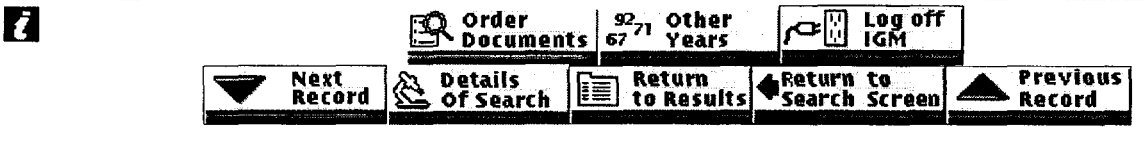
LANGUAGE: Jpn

REGISTRY NUMBERS: 107-35-7 (Taurine)
1115-84-0 (Vitamin U)
56-84-8 (Aspartic Acid)
56-85-9 (Glutamine)

National Library of Medicine: IGM Full Record Screen



TITLE:	Liquid chromatographic determination of taurine in vitamin premix formulations.
AUTHOR:	Rao GN
AUTHOR AFFILIATION:	Abbott Laboratories, Pharmaceutical Products Division, North Chicago, IL 60064.
SOURCE:	J Assoc Off Anal Chem 1987 Sep-Oct;70(5):799-801
NLM CIT. ID:	88058663
ABSTRACT:	A liquid chromatographic (LC) method is described for the determination of taurine in vitamin and vitamin-mineral premix formulations. The method involves extraction of taurine with 0.1 M bicarbonate buffer, followed by precolumn derivatization with dansyl chloride and LC using fluorescence detection. 6-Aminocaproic acid is used as an internal standard. A reverse phase analytical column and a mobile phase of 0.1 M acetate buffer solution (pH 7.2)-acetonitrile (75 + 25) are used. Vitamins, minerals, and other excipients in the premix formulations do not interfere in the determination. The method is simple, precise, and accurate.
MAIN MESH SUBJECTS:	Taurine/*ANALYSIS
	Vitamins/*ANALYSIS
ADDITIONAL MESH SUBJECTS:	Chemistry, Pharmaceutical
	Chromatography, Liquid
	Drug Stability
	Hydrogen-Ion Concentration
	Spectrometry, Fluorescence
	Temperature
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Vitamins)
	107-35-7 (Taurine)




Next Record
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Return to Search Screen
Previous Record

Title

Taurine-supplemented total ***parenteral nutrition*** and ***taurine*** status of malnourished cancer patients.

Author

Gray GE; Landel AM; Meguid MM

Address

Department of Surgery' University Hospital' SUNY Health Science Center' Syracuse 13210.

Source

Nutrition, 10(1):11-5 1994 Jan-Feb

Abstract

The status of plasma ***taurine*** and whether its concentration can be influenced by total ***parenteral nutrition*** (TPN) was determined in 51 malnourished fasting cancer patients after surgery and 7-14 days after starting TPN providing 41 +/- 2 kcal' 0.30 +/- 0.02 g N kg-1.day-1 and 40 mg pyridoxine. Plasma ***taurine*** was 50% lower in patients than in control subJects. Plasma ***taurine*** was significantly greater than baseline only after 14 days of TPN. We also studied the effects of surgery and ***taurine*** supplementation (8.6 mg.kg-1.day-1) on plasma and urine ***taurine*** concentrations in 12 malnourished patients. Preoperatively' all patients had normal plasma ***taurine*** concentrations; postoperatively' it was in the deficient range in 4 patients. ***Taurine***-supplemented patients initially had higher than baseline concentrations; by day 10' none had subnormal levels. Subnormal ***taurine*** concentrations commonly occur in malnourished postoperative cancer patients; surgery further precipitates their fall. Plasma concentrations were maintained only with ***taurine***-supplemented TPN.

Language

Eng

Unique Identifier

94257924

MESH Headings

Adult 1 I; Aged 1 I; Cysteine 1 I BL; Female 3 I; Human 3 I; Male 3 I; Methionine 1 I BL; Middle Age 1 I; Neoplasms 1 I BL/*CO; ***Nutrition*** Disorders 1 I BL/*CO/*TH; ***Parenteral Nutrition***' Total 1 I */MT; Support' Non-U.S. Gov`t 3 I; ***Taurine*** 1 I *AD/*BL/DF

Publication Type

CLINICAL TRIAL; JOURNAL ARTICLE; RANDOMIZED CONTROLLED TRIAL

ISSN

0899-9007

Country of Publication

UNITED STATES

Title

Effect of intravenous ***taurine*** supplementation on plasma' blood cell' and urine ***taurine*** concentrations in adults undergoing long-term ***parenteral nutrition***.

Author

Kopple JD; Vinton NE; Laidlaw SA; Ament ME

Address

Department of Medicine' School of Medicine' UCLA' Torrance 90509.

Source

Am J Clin Nutr, 52(5):846-53 1990 Nov

Abstract

Thirty-four adults undergoing long-term ***parenteral nutrition*** (TPN) were treated either with or without intravenous ***taurine*** for less than or equal to 24 mo. Statistical comparisons were carried out in eight patients randomly assigned to receive intravenous ***taurine***' usually 10 mg.kg-1.d-1' and 10 patients not receiving ***taurine***. Compared with normal adults' baseline plasma ***taurine*** and urine ***taurine***-creatinine ratios were decreased in both groups and platelet ***taurine*** was reduced in the ***taurine***-treated group. During ***taurine*** treatment the mean of the mean values for ***taurine*** became normal in plasma and platelets and remained normal in erythrocytes' granulocytes' and lymphocytes; urine ***taurine***-creatinine ratios rose to approximately five times normal. During follow-up' patients not given ***taurine*** had plasma' erythrocyte' and granulocyte ***taurine*** and urine ***taurine***-creatinine ratios below normal values and the concentrations of ***taurine***-treated patients. Their platelet ***taurine*** was also subnormal. Thus' 10 mg ***taurine***.kg-1.d-1 intravenously normalizes plasma and blood cell ***taurine*** concentrations in long-term TPN patients.

Candidates for Bulk Drug List - FDA Modernization Act
Pharmacy Compounding

Bulk Drug Information

Ingredient Name: **Glutamine**

Chemical Name: 2-aminoglutaramic acid

Common Name: Glutamine

Chemical Grade: Per specifications attached

How Supplied: Powder

Foreign Pharmacopeia Status: Is not listed in EP nor JP

Submitted previously to USP: Unknown

Safety and Efficacy data bibliography: See attached summaries

Compounded Product Information

Dosage Form: Sterile Injectable Solution

Strength: Approximately 2% solution of Glutamine in Sterile Water for Injection to be further diluted with Total Parenteral Nutrition (TPN) Solution prior to administration for a total dose of 25 mg to 400 mg/ Kg body wt/ day

Route of Administration: Intravenous (IV)

Information on past and proposed uses; rationale for use: See attached articles and JPEN, Volume 14 (No.4), July-August 1990 Supp.; pages 39S - 146S.

Why not use commercially available source?: Not available as a commercially available sterile solution supplement

Stability Data: See attached article. Conservatively assigned 2 weeks expiration dating at refrigerated temperatures. The data suggests that at 4 weeks held at 8 degrees C there is less than 5% change.

AJINOMOTO.

Caution : For Manufacturing , Processing or Repacking
Store in a dry place away from moisture and strong odors

L-グルタミン

L-GLUTAMINE

LOT NO. 301AABZ
NET 1 KG

C020461860311 35J01 2

L-GLU(NH2)

東京都中央区京橋1の15の1 味の素株式会社

AJINOMOTO CO.,INC. TOKYO

Made in Japan

19

AJINOMOTO

2046186/031. 13 指図書

PRODUCT DATA

AJINOMOTO CO., INC.
KAWASAKI PLANT
1-1 SUZUKI-CHO KAWASAKI-KU
KAWASAKI-CITY JAPAN

ANALYTICAL RESULTS OF L-GLUTAMINE

LOT NO. S01AABZ

Pyrogen	: Nonpyrogenic

MEMO : AJI USA

KAWASAKI PLANT
H. TANAKA

END

FOR AJINOMOTO U.S.A., INC.

2046186/031. 13 指図課

AJINOMOTO

PAGE 1
MAY. 24, 1994

PRODUCT DATA

AJINOMOTO CO., INC.
KAWASAKI PLANT
1-1 SUZUKI-CHO KAWASAKI-KU
KAWASAKI-CITY JAPAN

ANALYTICAL RESULTS OF L-GLUTAMINE

LOT NO. 301AABZ

Identification	: Passed test		
Specific rotation (D-LINE, 20°)	: 35.3 °		
AJI TEST1 dried sample, C=2. 6N HCl			
State of solution (Transmittance)	: NOT LESS THAN	98.0	%
AJI TEST2 0.4g in 20ml of H2O, spectrophotometer, 430nm, 10mm cell thickness			
State of solution	: Clear & colorless		
Chloride(Cl)	: NOT MORE THAN	0.020	%
Ammonium(NH4)	: NOT MORE THAN	0.10	%
Sulfate(SO4)	: NOT MORE THAN	0.020	%
Iron(Fe)	: NOT MORE THAN	10	PPM
Heavy metals(Pb)	: NOT MORE THAN	10	PPM
Arsenic(As2O3)	: NOT MORE THAN	1	PPM
Other amino acids	: Passed test		
AJI TEST9 test sample:30MCG, D-2-d control:L-Glu(NH2) 0.12MCG			
Loss on drying	: 0.01	%	
AJI TEST11 at 105° for 3hours			
Residue on ignition (sulfated)	: 0.01	%	
Assay	: 100.3	%	
PH	: 5.7		
AJI TEST33 1.0g in 50ml of H2O			

gd

CONT

National Library of Medicine: IGM Full Record Screen

TITLE: Safety and efficacy of increasing dosages of glycyl-glutamine for total parenteral nutrition in polytrauma patients.

AUTHOR: Weingartmann G; Fridrich P; Mauritz W; Gotzinger P; Mittlbock M; Germann P; Karner J; Roth E

AUTHOR AFFILIATION: Department of Medical Computer Sciences, AKH, University of Vienna.

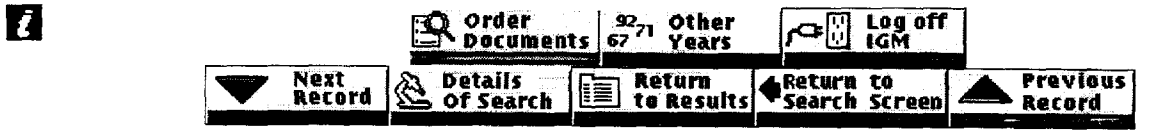
SOURCE: Wien Klin Wochenschr 1996;108(21):683-8

NLM CIT. ID: 97114768

ABSTRACT: Supplementation of parenteral nutrition with glutamine (GLN) has been suggested to improve the efficacy of nutritional support by stimulating protein synthesis and improving immunocompetence. In the present study we investigated the impact of infusing the dipeptide glycyl-glutamine (GLY-GLN) at increasing dosages on plasma amino acid concentrations in patients with polytrauma. Nine polytraumatized patients were randomly assigned according their age and their trauma score to three experimental groups. Group 1 received 280, group II 450, and group III 570 mg GLY-GLN per kg body weight/day for a period of four days (3rd to 7th posttraumatic day), resulting in a maximum daily GLN administration (calculated for a 70 kg patient) of 14 g, 21 g and 28 g, respectively. Seven polytraumatized patients receiving the nutrition solution without GLY-GLN supplementation served as controls. All patients received total parenteral nutrition with an average amino acid administration of 1.1 g/kg/day and a total energy intake of 30 kcal/kg/day. GLY-GLN infusion did not evoke any side effects. In comparison with the control group, arterial plasma GLN concentrations increased significantly on day I after start of infusion in groups II and III, but remained raised throughout the study period only in group III ($p < 0.003$). Similarly, plasma GLY concentrations were also significantly raised in group III ($p < 0.04$). The maximum increase of plasma GLY was found on the second infusion day, after which plasma concentrations of GLY fell to concentrations even below those observed in the control group at the end of the study period. Excretion of GLY-GLN, GLN or GLY in the urine during the GLY-GLN infusions was negligible. We conclude from this first available dose finding study on glutamine-containing dipeptides that in polytraumatized patients infusion of 570 mg/kg/day of GLY-GLN (corresponding to 28 g glutamine or 40 g dipeptide/70 kg, respectively) is necessary to induce a sustained effect on plasma glutamine concentrations. No pathological accumulation of free glycine or of the dipeptide was seen with any of the three dosage steps of GLY-GLN. Thus, the administration of even high doses of GLY-GLN is feasible and safe in patients with polytrauma and is not associated with any relevant renal substrate loss.

MAIN MESH	*Critical Care
SUBJECTS:	Dipeptides/*ADMINISTRATION & DOSAGE/BLOOD
	Multiple Trauma/BLOOD/*THERAPY
	*Parenteral Nutrition, Total
ADDITIONAL	Adult
MESH	Amino Acids/BLOOD
SUBJECTS:	Comparative Study
	Dose-Response Relationship, Drug
	Drug Administration Schedule
	Energy Intake/PHYSIOLOGY
	Female
	Glutamine/BLOOD
	Human
	Male
	Middle Age
PUBLICATION	CLINICAL TRIAL
TYPES:	JOURNAL ARTICLE
	RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	Eng
REGISTRY	0 (Amino Acids)
NUMBERS:	0 (Dipeptides)
	13115-71-4 (glycylglutamine)
	56-85-9 (Glutamine)

National Library of Medicine: IGM Full Record Screen



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TITLE: The effects of glutamine-supplemented parenteral nutrition in premature infants.

AUTHOR: Lacey JM; Crouch JB; Benfell K; Ringer SA; Wilmore CK; Maguire D; Wilmore DW

AUTHOR AFFILIATION: Laboratory for Surgical Metabolism and Nutrition, Brigham and Women's Hospital, Boston, MA 02115, USA.

SOURCE: JPEN J Parenter Enteral Nutr 1996 Jan-Feb;20(1):74-80

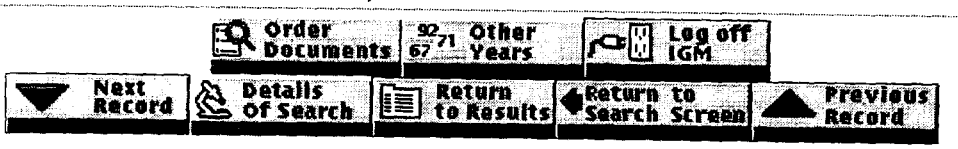
NLM CIT. ID: 96380255

ABSTRACT: BACKGROUND: Glutamine (GLN) is the primary fuel for rapidly dividing cells, yet it is not a constituent of parenteral nutritional formulas administered to newborns. The aims of this prospective, randomized, double-blind trial were (1) to confirm the safety of glutamine supplementation for premature infants and (2) to examine the effects of glutamine-supplemented parenteral nutrition on length of stay, days on total parenteral nutrition (TPN), days on the ventilator, and other clinical outcomes. METHODS: Premature infants received either standard or glutamine-supplemented TPN and were monitored throughout length of stay for various health and biochemical indices. The group was examined as a whole (n = 44; birth weight range: 530 to 1250 g) and in two weight subgroups, < 800 and > or = 800 g. RESULTS: Serum ammonia, blood urea nitrogen, and glutamate tended to be higher in the GLN groups, but the levels were well within normal limits. In the < 800-g cohort (n = 24), glutamine-supplemented infants required fewer days on TPN (13 vs 21 days, p = .02), had a shorter length of time to full feeds (8 vs 14 days, p = .03), and needed less time on the ventilator (38 vs 47 days, p = .04). There was a tendency toward a shorter length of stay in the NICU (73 vs 90 days, NS). These findings were not observed in the infants > or = 800 g (n = 20). CONCLUSIONS: Glutamine appears to be safe for use in premature infants and seems to be conditionally essential in premature infants with extremely low birth weights. Larger multicenter trials are needed to confirm these observations and further evaluate the efficacy of GLN in these high-risk premature infants.

MAIN MESH SUBJECTS: Glutamine/*ADMINISTRATION & DOSAGE/BLOOD
*Infant, Premature
*Parenteral Nutrition, Total

ADDITIONAL MESH SUBJECTS: Birth Weight
Blood Urea Nitrogen
Double-Blind Method
Female
Gestational Age
Glutamic Acid/BLOOD

	Human
	Infant, Newborn
	Male
	Prospective Studies
	Support, Non-U.S. Gov't
PUBLICATION TYPES:	**CLINICAL TRIAL**
	JOURNAL ARTICLE
	RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**56-85-9 (Glutamine)**
	56-86-0 (Glutamic Acid)



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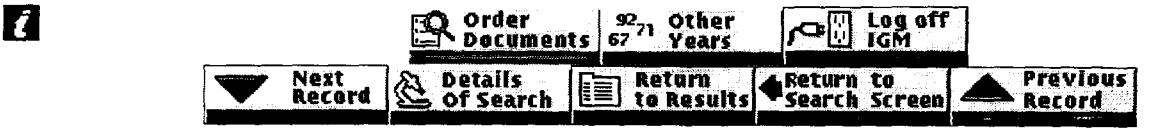


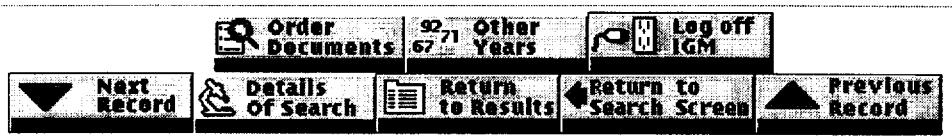
TITLE: Effect of parenteral L-glutamine on muscle in the very severely ill.
AUTHOR: Palmer TE; Griffiths RD; Jones C
AUTHOR AFFILIATION: Department of Medicine, University of Liverpool, UK.
SOURCE: Nutrition 1996 May;12(5):316-20
NLM CIT. ID: 97029504

ABSTRACT: Glutamine (Gln)-supplemented perioperative total parenteral nutrition (TPN) has been reported to reduce the loss of intramuscular glutamine following routine surgery. This study investigates whether glutamine-supplemented TPN can alter muscle biochemistry acutely in the very severely ill patient. Thirty-eight patients (age 19-77 yr; mean 55 yr), critically ill (APACHE II range 8-31; median 17) admitted to the intensive care unit (ICU) were recruited to receive either conventional TPN (CTPN) or an isonitrogenous, isoenergetic feed supplemented with 25 g crystalline L-glutamine per 24 h (GTPN) in a prospective, double blind, block-randomized study. In a representative sample of these patients, relatives consented to a paired muscle biopsy taken before feeding (10 GTPN/9 CTPN patients; ICU Day 2-4) and repeated 5 days later (16 patients; ICU Day 7-9). Muscle biopsies and matching plasma samples were analyzed using a coupled glutaminase-glutamate dehydrogenase enzymatic assay. A correction was made using sodium to account for the massive changes in extracellular fluid volume. The average muscle Gln content before feeding was very low. Between biopsies no consistent pattern of change was seen with or without exogenous Gln. It also proved difficult in these very sick patients to correct a low plasma Gln with L-Gln-TPN during the initial phase of the severe illness. TPN supplementation with 25 g/24 h, L-glutamine appears inadequate in the acute period to counteract the muscle and plasma biochemical changes seen in these patients. It is unknown whether any larger dose could alter this state.

MAIN MESH SUBJECTS: Critical Illness/*THERAPY
Glutamine/*ADMINISTRATION & DOSAGE/BLOOD/METABOLISM
Muscles/*CHEMISTRY/METABOLISM
*Parenteral Nutrition, Total

ADDITIONAL MESH SUBJECTS: Adult
Aged
Biopsy
Cohort Studies
Double-Blind Method
Human
Middle Age
Prospective Studies

Treatment Outcome
PUBLICATION TYPES: **CLINICAL TRIAL**
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL
LANGUAGE: **Eng**
REGISTRY NUMBERS: **56-85-9 (Glutamine)**



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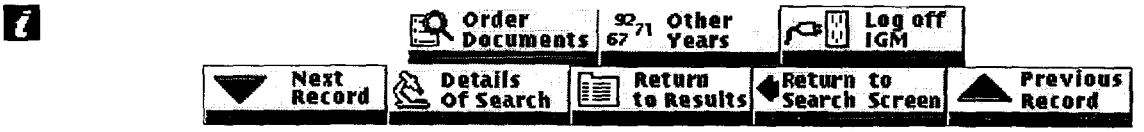


TITLE: Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study.

AUTHOR: Morlion BJ; Stehle P; Wachtler P; Siedhoff HP; Koller M; Konig W; Furst P; Puchstein C

AUTHOR AFFILIATION: Department of Anesthesiology and Intensive Care Medicine, Marienhospital Herne, Ruhr-University of Bochum, Germany.

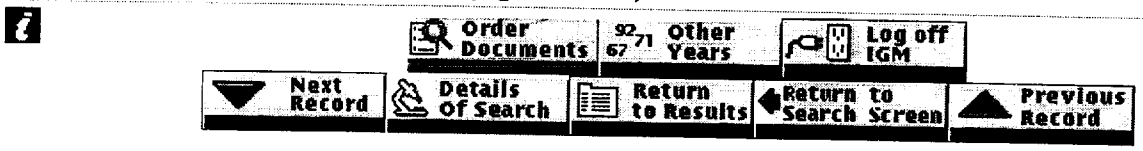
SOURCE: Ann Surg 1998 Feb;227(2):302-8

NLM CIT. ID: 98147855

ABSTRACT: OBJECTIVE: To assess the efficacy of glutamine (Gln) dipeptide-enriched total parenteral nutrition (TPN) on selected metabolic, immunologic, and clinical variables in surgical patients. SUMMARY BACKGROUND DATA: Depletion of Gln stores might lead to severe clinical complications. Recent studies indicate that the parenteral provision of Gln or Gln-containing dipeptides improves nitrogen balance, maintains the intracellular Gln pool, preserves intestinal permeability and absorption, and shortens hospital stay. METHODS: Twenty-eight patients (age range, 42-86 years, mean 68 years) undergoing elective abdominal surgery were allocated, after randomization, to two groups to receive isonitrogenous (0.24 g nitrogen kg(-1) day(-1)) and isoenergetic (29 kcal/122 kJ kg(-1) day(-1)) TPN over 5 days. Controls received 1.5 g of amino acids kg(-1) day(-1), and the test group received 1.2 g of amino acids and 0.3 g of L-alanyl-L-glutamine (Ala-Gln) kg(-1) day(-1). Venous heparinized blood samples were obtained before surgery and on days 1, 3, and 6 after surgery for routine clinical chemistry and for the measurement of plasma free amino acids. Lymphocytes were counted and the generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes was analyzed before surgery and on days 1 and 6 after surgery. Nitrogen balances were calculated postoperatively on days 2, 3, 4, and 5. RESULTS: No side effects or complaints were noted. Patients receiving Gln dipeptide revealed improved nitrogen balances (cumulative balance over 5 days: -7.9 +/- 3.6 vs. -23.0 +/- 2.6 g nitrogen), improved lymphocyte recovery on day 6 (2.41 +/- 0.27 vs. 1.52 +/- 0.17 lymphocytes/nL) and improved generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes (25.7 +/- 4.89 vs. 5.03 +/- 3.11 ng/mL). Postoperative hospital stay was 6.2 days shorter in the dipeptide-supplemented group. CONCLUSION: We confirm the beneficial effects of Gln dipeptide-supplemented TPN on nitrogen economy, maintenance of plasma Gln concentration, lymphocyte recovery, cysteinyl-leukotriene generation, and shortened hospital stay in surgical patients.

MAIN MESH SUBJECTS: Colonic Neoplasms/*SURGERY
*Dipeptides

	*Parenteral Nutrition, Total
	Rectal Neoplasms/*SURGERY
ADDITIONAL MESH SUBJECTS:	Adult
	Aged
	Aged, 80 and over
	Amino Acids/BLOOD
	Double-Blind Method
	Female
	Human
	Length of Stay
	Lymphocyte Count
	Male
	Middle Age
	Postoperative Period
	Stress/METABOLISM
	Support, Non-U.S. Gov't
PUBLICATION TYPES:	CLINICAL TRIAL
	JOURNAL ARTICLE
	RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Amino Acids)
	0 (Dipeptides)
	39537-23-0 (alanylglutamine)



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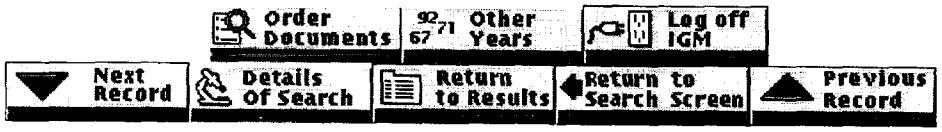
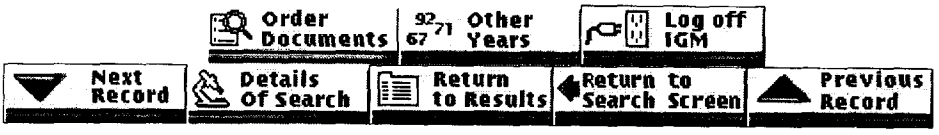


TITLE:	Historical perspective on nutritional support of cancer patients [editorial; comment]
AUTHOR:	Copeland EM 3rd
SOURCE:	CA Cancer J Clin 1998 Mar-Apr;48(2):67-8
NLM CIT. ID:	98183365
COMMENT:	CA Cancer J Clin 1998 Mar-Apr;48(2):69-80
ABSTRACT:	Initially, total parenteral nutrition (TPN) was not used in cancer patients because of the fear of sepsis and the potential for stimulation of tumor growth. It was used first in cancer patients who had failed all attempts at enteral nutrition and in whom adequate anticancer therapy would have been otherwise impossible. TPN candidates today remain patients with responsive tumors who cannot tolerate the toxicity of cancer therapy because they are malnourished.
MAIN MESH SUBJECTS:	Neoplasms/DRUG THERAPY/PHYSIOPATHOLOGY/*THERAPY *Parenteral Nutrition, Total/ADVERSE EFFECTS/INSTRUMENTATION
ADDITIONAL MESH SUBJECTS:	Antineoplastic Agents/PHARMACOLOGY/THERAPEUTIC USE Catheterization, Central Venous/ADVERSE EFFECTS/INSTRUMENTATION Catheters, Indwelling/ADVERSE EFFECTS Enteral Nutrition Glutamine/ADMINISTRATION & DOSAGE/THERAPEUTIC USE Human Nutrition Disorders/THERAPY Patient Selection Sepsis/ETIOLOGY
PUBLICATION TYPES:	COMMENT EDITORIAL
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Antineoplastic Agents) 56-85-9 (Glutamine)



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TITLE: Effect of glutamine-enriched total parenteral nutrition on small intestinal gut-associated lymphoid tissue and upper respiratory tract immunity.

AUTHOR: Li J; Kudsk KA; Janu P; Renegar KB
AUTHOR AFFILIATION: Department of Surgery, University of Tennessee at Memphis, USA.

SOURCE: Surgery 1997 May;121(5):542-9
NLM CIT. ID: 97287061

ABSTRACT: BACKGROUND: Our prior work shows that total parenteral nutrition (TPN) causes small intestinal gut-associated lymphoid tissue (GALT) atrophy, lowers small intestinal immunoglobulin A (IgA) levels, and impairs secretory IgA-mediated mucosal immunity of the upper respiratory tract. These experiments examine whether an isonitrogenous 2% glutamine-enriched TPN solution prevents these changes. METHODS: Institute of Cancer Research mice were randomized to chow (chow), intravenous feeding of a TPN solution (TPN), or glutamine-enriched TPN (glutamine) groups. After mice were fed for 5 days, lymphocytes were isolated from Peyer's patches, the intraepithelial layer, and lamina propria to determine cell yields and phenotypes. Total small intestinal IgA levels were analyzed by means of enzyme-linked immunosorbent assay. In a second series of experiments, mice underwent intranasal inoculation with H1N1 virus to establish immunity. After 3 weeks mice were randomized to chow, TPN, or glutamine groups. After feeding for 5 days, mice were rechallenged with intranasal virus and killed at 40 hours to determine viral shedding from the upper respiratory tract. RESULTS: Total lymphocyte yield in the Peyer's patches, the intraepithelial layer, and lamina propria, small intestinal IgA levels, and the CD4+/CD8+ ratio in the lamina propria decreased with TPN but remained normal with glutamine. On rechallenge, 87% of the mice in the TPN group shed virus in nasal secretions, whereas only 38% of the glutamine-treated group ($p < 0.05$ versus TPN) and 7.1% of the chow group ($p < 0.002$ versus TPN) were virus positive. CONCLUSIONS: Isonitrogenous supplementation of TPN with 2% glutamine improves IgA-mediated protection in the upper respiratory tract and normalizes GALT populations.

MAIN MESH SUBJECTS: Glutamine/ADMINISTRATION & DOSAGE/*PHARMACOLOGY
Nasal Mucosa/DRUG EFFECTS/*IMMUNOLOGY
*Parenteral Nutrition, Total
Peyer's Patches/DRUG EFFECTS/*IMMUNOLOGY
ADDITIONAL MESH SUBJECTS: Animal
IgA/ANALYSIS
Lymphocyte Count
Mice

Nasal Lavage Fluid/VIROLOGY
Virus Shedding
PUBLICATION TYPES: **JOURNAL ARTICLE**
LANGUAGE: **Eng**
REGISTRY NUMBERS: **0 (IgA)**
56-85-9 (Glutamine)

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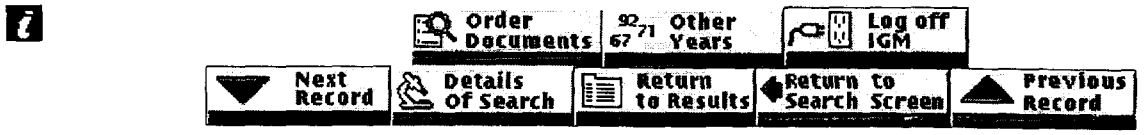


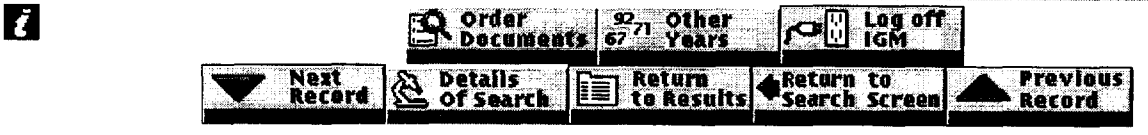
TITLE:	Glutamine and intestinal immune cells in humans.
AUTHOR:	van der Hulst RR; von Meyenfeldt MF; Tiebosch A; Buurman WA; Soeters PB
AUTHOR AFFILIATION:	Department of Surgery, University of Limburg, Maastricht, The Netherlands.
SOURCE:	JPEN J Parenter Enteral Nutr 1997 Nov-Dec;21(6):310-5
NLM CIT. ID:	98069200
ABSTRACT:	BACKGROUND: Total parenteral nutrition (TPN) is associated with depletion of intestinal immune cells and increased gut permeability (GP). Adding glutamine (GLN) to TPN preserves GP by an unknown mechanism. Intestinal immune cells situated between the enterocytes (intraepithelial lymphocytes, [IEL]) influence GP in vitro. To obtain insight into the underlying mechanism of GLN on GP, we investigated the effects of GLN-supplemented TPN on IEL, immunoglobulin A (IgA) plasma cells and goblet cells, and enterocyte proliferation in intestinal biopsies. METHODS: Twenty patients randomly received GLN-enriched TPN (GT) or isonitrogenous standard TPN (ST). Proliferation and number of immune cells were measured in intestinal biopsies obtained before and after 10 days of TPN. RESULTS: No change in proliferative activity or in number of IgA plasma cells was observed. Goblet cells increased in the ST group, whereas the change seen in the GT group did not reach significance. In the GT group, IEL decreased, whereas in the ST group, no change in the number of IEL was observed. CONCLUSIONS: TPN was not associated with changes in proliferative activity or with depletion of gut immune cells. The data indicate that GLN-supplemented TPN has a different effect on intestinal immune cells compared with standard TPN.
MAIN MESH SUBJECTS:	Epithelial Cells/*DRUG EFFECTS/METABOLISM Glutamine/*PHARMACOLOGY IgA/*BIOSYNTHESIS Intestinal Mucosa/*DRUG EFFECTS/PATHOLOGY Lymphocytes/*DRUG EFFECTS/METABOLISM *Parenteral Nutrition Plasma Cells/*DRUG EFFECTS/METABOLISM
ADDITIONAL MESH SUBJECTS:	Adolescence Adult Aged Amino Acids/PHARMACOLOGY Antibody Formation/DRUG EFFECTS Cell Division/DRUG EFFECTS Comparative Study

Female
Human
Immunity, Cellular/DRUG EFFECTS
Lymphocyte Count
Male
Middle Age
Mucus/METABOLISM

PUBLICATION TYPES: **CLINICAL TRIAL**
JOURNAL ARTICLE
RANDOMIZED CONTROLLED TRIAL

LANGUAGE: **Eng**

REGISTRY NUMBERS: **0 (Amino Acids)**
0 (IgA)
56-85-9 (Glutamine)



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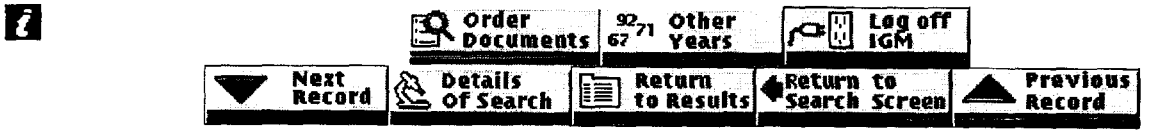

TITLE: Glycyl-L-glutamine-enriched total parenteral nutrition maintains small intestine gut-associated lymphoid tissue and upper respiratory tract immunity.

AUTHOR: Li J; King BK; Janu PG; Renegar KB; Kudsk KA

AUTHOR AFFILIATION: Department of Surgery, University of Tennessee at Memphis 38163, USA.

SOURCE: JPEN J Parenter Enteral Nutr 1998 Jan-Feb;22(1):31-6

NLM CIT. ID: 98100306

ABSTRACT: BACKGROUND: i.v. administration of a total parenteral nutrition (TPN) solution results in small intestinal gut-associated lymphoid tissue (GALT) atrophy, lowers small intestinal immunoglobulin A (IgA) levels, and impairs upper respiratory tract secretory IgA-mediated mucosal immunity; isonitrogenous supplementation of TPN with 2% glutamine attenuates these changes. This experiment examines whether a 2% glycyl-L-glutamine-enriched TPN solution reverses i.v. TPN-induced changes as effectively as L-glutamine. METHODS: Male Institute of Cancer Research (ICR) mice underwent intranasal inoculation with H1N1 influenza virus to establish immunity. After 3 weeks, mice were randomized to chow, i.v. feeding of a TPN solution, glutamine-enriched TPN, or glycyl-L-glutamine-enriched TPN. After 4 days of feeding, mice were challenged intranasally with influenza virus and killed at 40 hours to determine viral shedding from the respiratory tract; normal convalescent mice do not shed virus because they possess intact IgA-mediated mechanisms Lymphocytes were isolated from Peyer's patches, the intraepithelial layer, and lamina propria to determine cell yields. RESULTS: Total lymphocyte yield in the Peyer's patches, the intraepithelial layer, and lamina propria decreased with TPN but remained normal with glutamine and glycyl-L-glutamine. Upon challenge, 70% of the mice in the TPN group shed virus in nasal secretions, whereas only 20% of the glutamine-treated group, 18% of glycyl-L-glutamine group and none of the Chow group were virus positive. CONCLUSIONS: L-Glutamine and glycyl-L-glutamine have similar effects on i.v. administered TPN-associated (GALT) atrophy and decreased upper respiratory tract immunity.

MAIN MESH SUBJECTS: Dipeptides/*ADMINISTRATION & DOSAGE
Intestine, Small/*IMMUNOLOGY
*Parenteral Nutrition, Total
Peyer's Patches/CYTOLOGY/*IMMUNOLOGY/PATHOLOGY
Respiratory System/*IMMUNOLOGY
Virus Shedding/*IMMUNOLOGY

ADDITIONAL MESH SUBJECTS: Animal
Animal Nutrition
Comparative Study

Glutamine/ADMINISTRATION & DOSAGE
Influenza A Virus, Human/PATHOGENICITY
Lymphocytes/IMMUNOLOGY
Male
Mice
Mice, Inbred ICR
Random Allocation
Support, Non-U.S. Gov't

PUBLICATION TYPES: **JOURNAL ARTICLE**

LANGUAGE: **Eng**

REGISTRY NUMBERS: **0 (Dipeptides)**
13115-71-4 (glycylglutamine)
56-85-9 (Glutamine)

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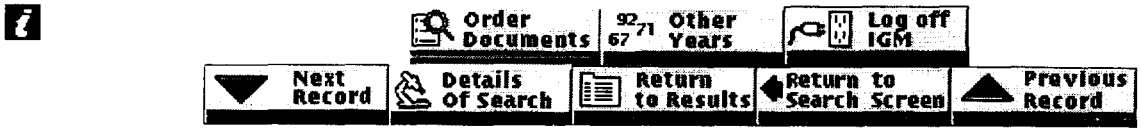

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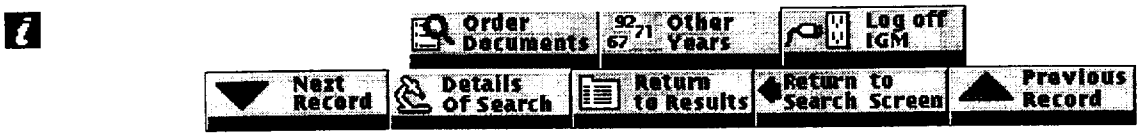
TITLE:	Brief clinical report: glutamine-enriched total parenteral nutrition in a patient with radiation-induced renal and intestinal fibrosis.
AUTHOR:	Wicke C; Gottwald T; Becker HD
AUTHOR AFFILIATION:	Department of General Surgery, University of Tubingen, Germany.
SOURCE:	Nutrition 1996 Nov-Dec;12(11-12 Suppl):S85-6
NLM CIT. ID:	97129619
ABSTRACT:	This brief clinical report illustrates the case of a 50-y-old male patient with severe radiation-induced renal and intestinal fibrosis who received glutamine-enriched total parenteral nutrition (TPN). The patient had end-stage renal disease and, therefore, underwent a kidney transplant. In the postoperative course the patient developed signs of bowel obstruction and cachexia. He received two courses of glutamine-enriched TPN before he underwent surgery for small bowel stenosis. Postoperatively, the patient received a third course of glutamine-enriched TPN. During the patient's hospital course the following indexes were monitored: patient's weight, serum concentrations of protein, albumin, and trialglycerol. Intestinal permeability was assessed with the lactulose-mannitol sugar test (L-M test). We measured changes in the patient's weight and the L-M test. We hypothesize that glutamine-enriched TPN may have been beneficial in the hospital course of this critically ill patient and may have influenced the patient's intestinal function and permeability.
MAIN MESH SUBJECTS:	Glutamine/*ADMINISTRATION & DOSAGE Intestines/*PATHOLOGY/RADIATION EFFECTS Kidney/*PATHOLOGY/RADIATION EFFECTS *Parenteral Nutrition, Total *Radiation Injuries
ADDITIONAL MESH SUBJECTS:	Case Report Fibrosis Human Kidney Failure, Chronic/SURGERY Kidney Transplantation Male Middle Age
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	56-85-9 (Glutamine)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amino acid stability in aqueous solutions of casein hydrolysate under varied storage conditions

by JOHN E. FRIEND, LEWIS D. STEGINK *and* DUANE E. KANN

► PROTEIN HYDROLYSATES HAVE BEEN UTILIZED FOR parenteral alimentation for over 75 years[1] in attempts to obtain a positive nitrogen balance and a net protein synthesis in patients unable to take nutrients by mouth. Protein hydrolysate alimentation currently has reached a new plateau of popularity through the efforts of Wilmore and Dudrick.[2-10] The formulation modifications and acceptable administration route developed by these investigators highlighted parenteral alimentation as a rational replacement for oral alimentation in certain types of patients.

There appears to be much value in the administration of protein hydrolysate or crystalline amino acid solutions to seriously ill patients. From the pharmaceutical point of view, it is important to consider the stability of protein hydrolysates (i.e., amino acids) in solution.

JOHN E. FRIEND, M.S., was a graduate student, College of Pharmacy, The University of Iowa, during the tenure of this work; he is currently Senior Clinical Research Coordinator, Travenol Laboratories, Inc., Morton Grove, Illinois 60053. LEWIS D. STEGINK, Ph.D., is Associate Professor of Pediatrics and Biochemistry, The University of Iowa College of Medicine. DUANE E. KANN, M.S., is Instructor and Assistant Director of Pharmaceutical Services, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52240.

This paper was abstracted in part from the thesis submitted as partial fulfillment for the M.S. degree from the College of Pharmacy, The University of Iowa.

This research was supported in part by Travenol Laboratories, Inc.

Presented at the Sixth Annual Midyear Clinical Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, Washington, D.C., December 14, 1971.

An intensive literature search revealed little information concerning amino acid stability in protein hydrolysate solution when stored in aqueous solution. Since some of the amino acids which compose the major constituent of the protein hydrolysate solutions are potentially labile[11] upon storage, it is of interest to determine what effect storage time and temperature have upon the amino acid composition of such preparations. It is also important to determine the stability of certain other amino acids not present in current formulations, since such data will be needed for the development of new crystalline amino acid preparations. The study described in this paper details the stability of the amino acids present in casein hydrolysate solutions at various temperatures with increasing time. Several amino acids — glutamine, cystine, cysteine and tryptophan — which are either normally absent or present at very low levels in such mixtures but which may be present in crystalline amino acid formulations of the future were added to determine their stability as well.

Materials and Methods

A 5% (w/v) solution was prepared with a powdered enzymic hydrolysate of casein supplied by Travenol Laboratories, Inc. (Amigen). Since the hydrolysate was essentially devoid of glutamine, cystine and cysteine, and contained small amounts of tryptophan, additional quantities of each of these amino acids were added as the crystalline L-amino acids to give the amino acid composition shown in the "initial" value column of Table 1. This hydrolysate solution was sterilized by filtration through a 0.22 μ membrane filter. It was then placed aseptically in sterile vials under a laminar air flow hood, stoppered with sterile stoppers, capped and stored at 8, 23, 37 or 47 C.

Initially and after one, two, four, eight and twelve weeks of storage, individual vials were removed from the incubators and aliquots were analyzed for amino acid composition using Technicon NC-1 single column amino acid analyzers. The buffer system described by Efron[13] was utilized as described in our initial studies of the amino acid composition of protein hydrolysate solutions.[13]

Cysteine concentrations are difficult to measure using the amino acid analyzer,[14,15] thus we have measured cysteine concentrations using the method of Ellman.[16] Cystine concentrations were determined from the amino acid analyzer patterns. Since cysteine is eluted from the analyzer column at the same point as cystine, the values for cystine have been corrected for the amount of cysteine.

Tryptophan concentrations may be obtained from the amino acid analyzer chromatogram, however the peak height is small and the width is great, making accurate determinations difficult. Accordingly, tryptophan was measured using a modification of the fluorometric method of Duggan and Udenfriend.[17] In this method, 0.01 ml of the 5% casein hydrolysate solution is added to 8.0 ml of 0.5 M sodium carbonate and made to a final volume of 10.0 ml with distilled water. The fluoresence was measured using an Aminco-Bowman spectrophotofluorometer with an excitation wavelength of 283 mμ and an emission wavelength of 370 mμ. Because substantial quenching of fluoresence occurs due to other components of the hydrolysate, a nonlinear relationship between percent transmission and concentrations was obtained when aliquots greater than 0.01 ml were used. However, a linear relationship is obtained using 0.01 ml aliquots of the casein hydrolysate solution containing increasing concentrations of tryptophan as shown in Figure 1.

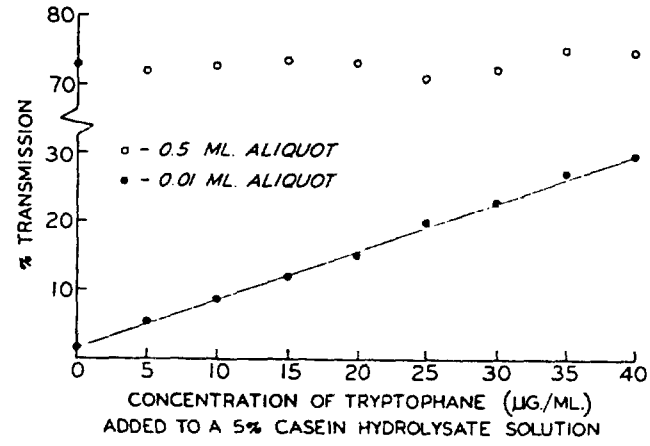


Figure 1. Relationship between tryptophan concentration in casein hydrolysate solution and fluorescent transmission

Results

The data shown in Table 1 demonstrate that most of the amino acids present in this mixture were stable over the 12-week period at all temperatures studied with the exception of glutamine, cysteine and cystine. Analyses at the intervening time intervals (one, two, four and eight weeks) confirmed the stability for each amino acid over the entire time period and provided a more detailed evaluation of the changes occurring in glutamine, cysteine and cystine.

The changes noted in the levels of glutamine, ammonia, cysteine, cystine and cysteic acid were expected to some extent. Studies by other investigators of the stability of glutamine in plasma samples had indicated the lability of glutamine in aqueous solution.[11,12] Glutamine may decompose to ammonia and either glutamate or pyrrolidone-5-carboxylate. These reactions are shown in Figure 2.

Table 1. Effect of Storage For 12 Weeks At Various Temperatures on Amino Acid Concentrations in Casein Hydrolysate Preparations[a]

	μmoles/ml				
AMINO ACID	INITIAL	8°	23°	37°	47°
Cysteic acid	1.1	1.5	1.7	1.5	1.2
Methionine sulfoxide	1.0	1.1	1.6	1.8	2.3
Aspartate	6.2	6.3	6.1	6.2	6.3
Threonine	12.2	11.3	11.8	12.0	11.7
Serine	19.7	20.5	19.5	20.0	19.7
Glutamine	18.1	13.4	6.5	0	0
Glutamate	24.0	22.7	21.8	23.2	22.1
Proline	18.9	19.9	19.8	19.4	19.1
Glycine	7.0	6.8	6.5	7.2	7.1
Alanine	13.9	13.3	13.0	13.8	13.3
Valine	18.8	18.9	18.6	20.1	20.0
Methionine	7.1	7.1	6.9	7.3	7.1
Isoleucine	12.8	13.2	12.7	13.3	13.6
Leucine	26.9	27.8	26.4	27.8	26.7
Tyrosine	2.1	2.3	2.0	2.2	2.3
Phenylalanine	10.2	10.6	9.7	10.2	10.3
Ammonia	25.8	30.2	39.4	43.0	45.0
Lysine	20.0	20.3	19.0	19.3	20.0
Histidine	6.2	5.9	5.7	5.8	5.7
Arginine	8.2	8.7	8.3	8.2	8.2
Cysteine	0.8	0.07	0.05	0.06	0.07
Cystine	0.67	1.4	1.2	1.5	1.4
Tryptophan	1.8	1.9	2.0	1.8	1.7

[a]Based on at least duplicate analyses.

The rate of glutamine lability at the various temperatures is shown in Figure 3. As expected, the reaction is most rapid at elevated temperatures. In addition, the release of ammonia (16 μmoles/ml) is directly proportional to the loss of glutamine (17 μmoles/ml) in these solutions. No increase in glutamate levels was noted, indicating that pyrrolidone-5-carboxylate is the major degradation product. This was confirmed by acid hydrolysis of the various casein hydrolysate mixtures, converting pyrrolidone-5-carboxylate into glutamate

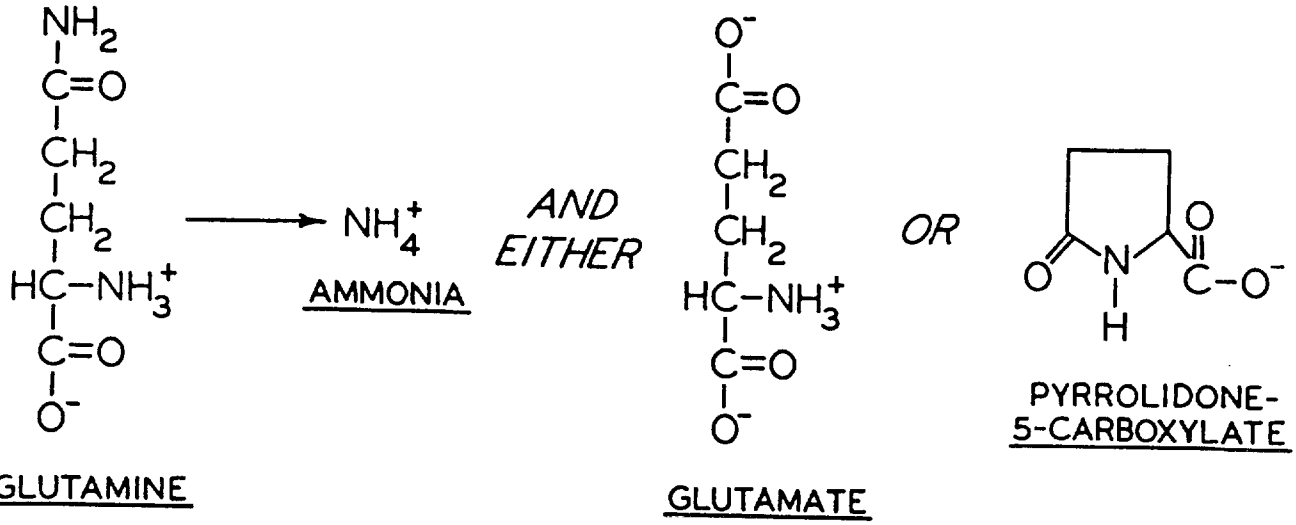
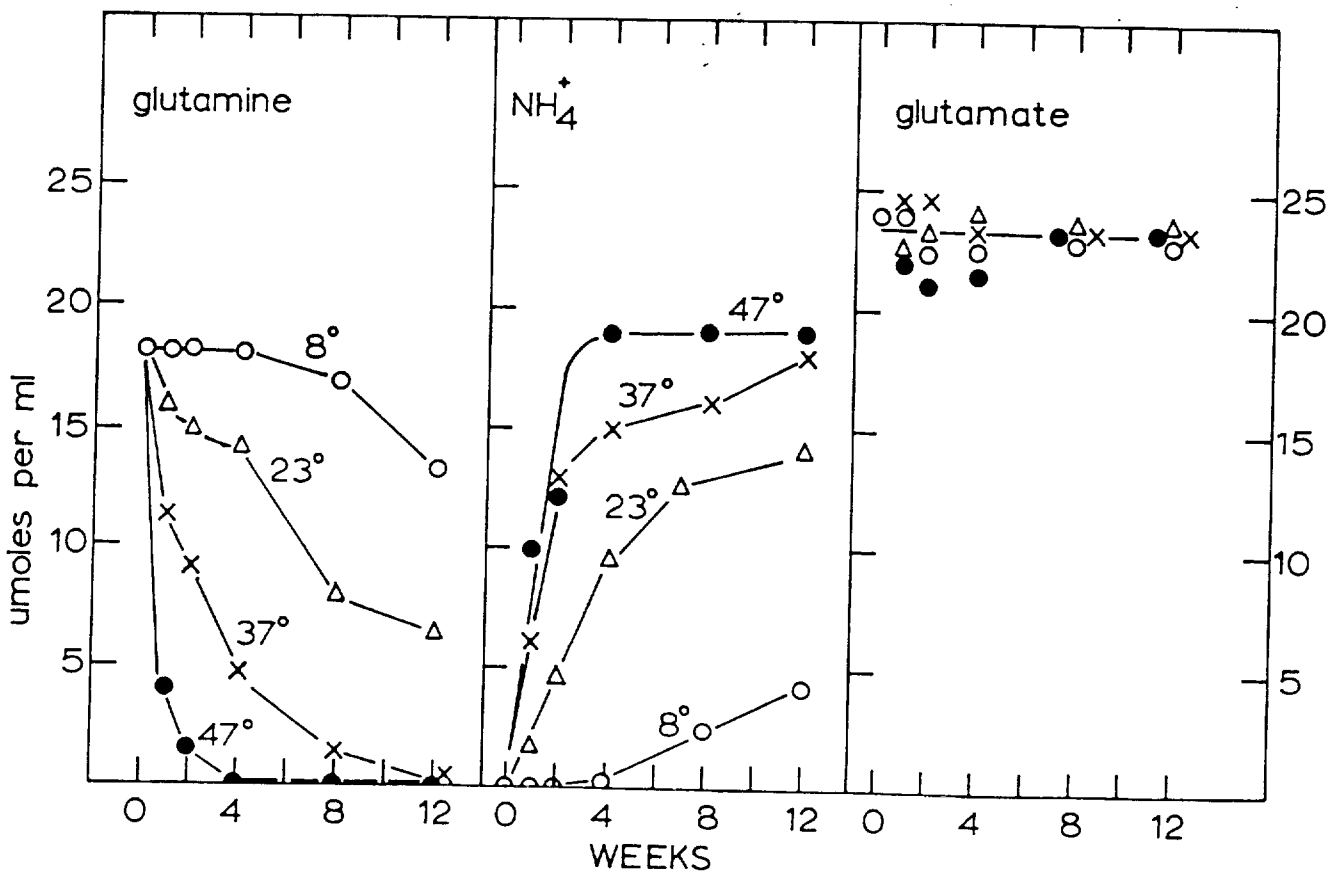


Figure 2. Glutamine degradation to ammonia and either glutamate or pyrrolidone-5-carboxylate

Figure 3. Concentrations of glutamine, ammonia and glutamate in casein hydrolysate solutions upon storage; note that ammonium ion concentrations refer to change in ammonium levels over baseline



which can be measured on the amino acid analyzer. In this manner it was possible to demonstrate an increase in glutamate levels equal to the loss of the added glutamine, supporting the conclusion that pyrrolidone-5-carboxylate is the major degradation product.

The loss of cysteine from the solution was also expected. Cysteine may be readily oxidized to form either cystine or cysteic acid as shown in Figure 4.

The data shown in Figure 5 demonstrate that regardless of temperature virtually all cysteine had been converted to cystine. Only small increases in cysteic acid levels were noted (see Table 1).

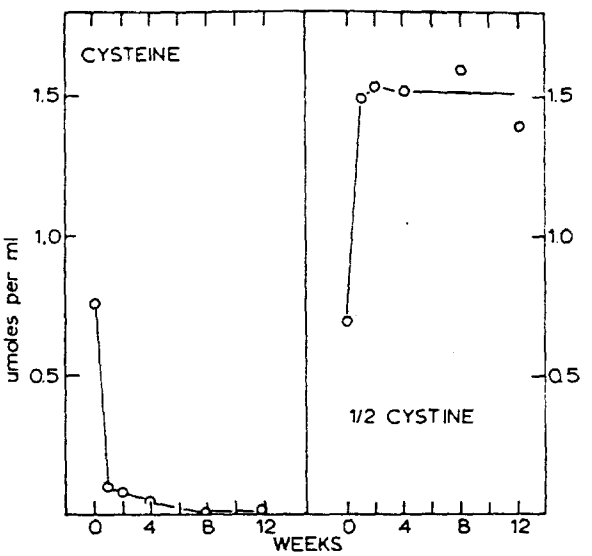


Figure 5. Concentrations of cysteine and cystine in casein hydrolysate solutions upon storage; no difference was noted between storage temperatures at these time intervals

Color Formation in Casein Hydrolysate Solution Test Samples

Casein hydrolysates develop a chromogen in aqueous solution. Figure 6 demonstrates the increasing pigmentation of the solution at eight weeks of storage at 8, 23, 37 and 47 C. Intensity of the chromogen was increased by prolonged storage and with elevated temperatures. The elevated temperature effect on chromogen formation was greater than the effect of prolonged storage.

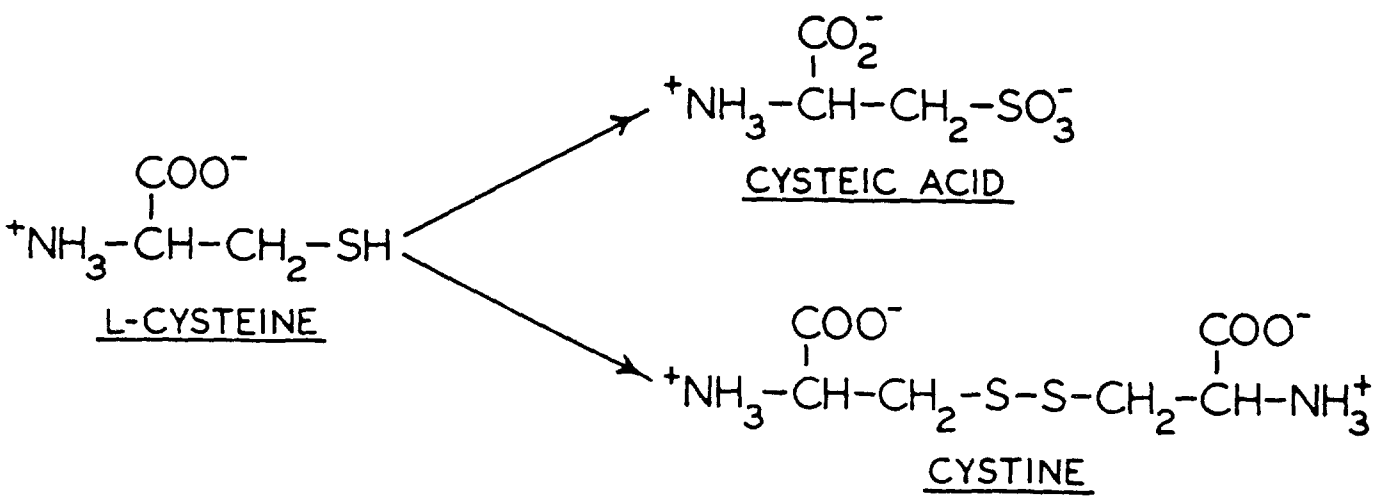
The appearance of a chromagen in protein hydrolysate solutions has been attributed to the presence of carbohydrate[19] and or cysteine.[20] When the casein hydrolysates were subjected to the phenolsulfuric acid reagent test for carbohydrates,[21] a definite positive reaction was obtained. Even though the quantity of carbohydrate and or related compounds found was quite small, it is possible that this material is the causative agent in the formation of the chromogen in the solution test samples. The effect of cysteine in casein hydrolysate solutions on the chromogen formation is being studied.

Discussion

The purpose of this study was to examine the stability of amino acids commonly found in protein hydrolysate powder which is suitable for the manufacturing of Protein Hydrolysate Injection, U.S.P. The amino acids normally present in the casein hydrolysate preparation demonstrated excellent stability at the various temperatures studied. However, glutamine and cysteine which were added to these preparations, and which would be useful additives for future parenteral alimentation mixtures, showed considerable lability in solution.

Glutamine degradation was relatively slow at 8 C for short periods of time, indicating that storage of future preparations containing this amino acid may be possible if stored at low temperatures.

Figure 4. Oxidation reactions of cysteine in solution



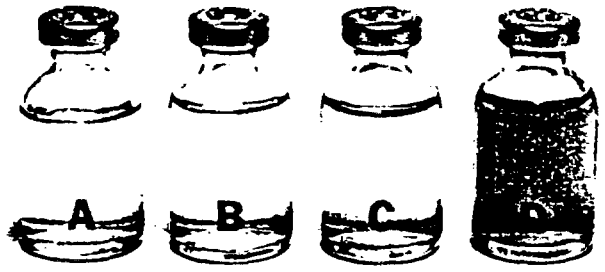


Figure 6. Chromogen formation in casein hydrolysate solutions stored for eight weeks at various temperatures: vial A stored at 8 C, vial B at 23 C, vial C at 37 C and vial D at 47 C

The conversion of cysteine into its disulfide form is rapid. Within one week virtually all cysteine is converted to cystine. This is unfortunate, since from the pediatrician's point of view supplementation of the current formulas with cystine or cysteine would seem a logical step forward because of (1) the evidence indicating that these amino acids may be essential for the premature infant and (2) their absence from current parenteral alimentation nitrogen sources.[13,22,23]

The conversion of cysteine into cystine is not necessarily a problem, since cystine is the form of the amino acid circulating in the plasma. However, from a manufacturing point of view, the insolubility of cystine presents problems.

We recently carried out an additional experiment in which we added cysteine to a protein hydrolysate and measured the disappearance of cysteine at 23 C for a shorter time period. Starting with an initial concentration of 3 μmoles/ml of cysteine at zero time, the concentration fell to 1.5 μmoles/ml at the end of 24 hours and to 1 μmoles/ml at the end of 48 hours. No precipitation was noted in the bottle. Thus, although a rapid conversion to cystine takes place, it may be possible to supplement current preparations with cysteine for future work over short time periods.

Amino acid racemization was not systematically investigated in this study. It is known that hydrolysis of proteins in strong acid at elevated temperatures results in a 2-4% racemization of the amino acids.[24-26] It seems unlikely that such racemization would be a problem at the low hydrogen ion concentrations (10^{-5} to 10^{-6}) and temperature present in these studies. We have made preliminary studies of the rate of methionine racemization in samples stored for two weeks at 23 C. No detectable amounts of D-methionine were found using the method of Stegink and Meyer.[27] Our clinical experience supports these chemical data indicating little racemization under normal storage conditions. The data of Clayton et al.[28] and that from our laboratory[29] demonstrate that the ingestion of D-amino acids, even when present as a low percentage of the total (2-4%[28]) results in aminoaciduria involving amino acids in question. Our clinical studies of pediatric and adult subjects infused with parenteral alimentation solutions using casein hydrolysate preparations as the nitrogen source give no indication of such aminoaciduria. However, it should be pointed out that alkaline storage conditions would cause considerable racemization of the amino acids.[26,30] It should also be pointed out that protein hydrolysate preparations made by acid hydrolysis of the protein do contain quantities of the D-amino acids. The casein hydrolysate preparation used in this study is produced by the enzymic hydrolysis of casein which avoids the racemization inherent in the acid hydrolysis procedure. Knowledge of the extent of amino acid racemization under varied storage conditions must await a more definitive study using methods specifically designed to detect low quantities of the D-isomers in the presence of large quantities of the L-isomers.

Conclusion

Only one lot of casein hydrolysate powder was studied for amino acid stability in aqueous solution. The casein hydrolysate test solution was not autoclaved, did not contain antioxidants, and was not stored under a vacuum as are commercial protein hydrolysate products.

It was found that added glutamine degraded to pyrrolidone-5-carboxylate and ammonia. The increased ammonia content may be related to the clinical situation of hyperammonemia which has been reported.[31]

Cysteine is converted to the disulfide form cystine. Since the term and premature infant may require these amino acids for nutrition, the limited solubility of cystine remains to be a problem area.

As an additional aspect of this study, we lyophilized the casein hydrolysate test solution and were able to increase the stability of the aforementioned amino acids. This study will be reported in next month's JOURNAL.

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ABSTRACT

The stability of amino acids in aqueous solutions of casein hydrolysate upon storage at various temperatures was examined.

A bulk solution prepared from casein hydrolysate was sterilized by filtration and filled into sterile vials which were stored at 8, 23, 37 and 47 C. Vials were analyzed initially and at the end of one, two, eight and 12 weeks of storage.

Glutamine was found to be readily degraded to pyrrolidone-5-carboxylate and ammonia, especially at the higher storage temperatures. Cysteine was found to be rapidly converted into cystine at all temperatures studied. No significant changes in the concentrations of the other amino acids were noted. The hydrolysate solutions develop a chromogen in aqueous solution, the intensity of which is increased by storage and by elevated temperatures. The temperature effect upon chromogen formation appears greater than the effect of prolonged storage.

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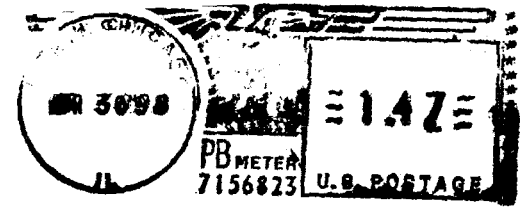

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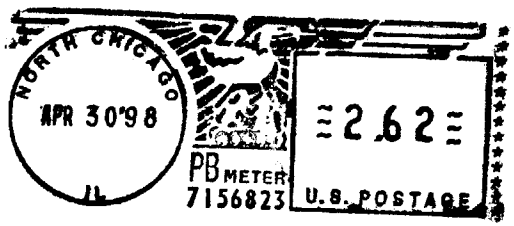

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